Remarks

The Official Action dated September 17, 2009 has been carefully reviewed. In view of the present amendments and following remarks, favorable reconsideration and allowance of this application are respectfully requested.

The sole issue remaining in this application is the maintained rejection of claims 9, 10, 12, 19, 22, 24, 27, 36, 37, 47 and 52 under 35 U.S.C. §112, first paragraph as allegedly failing to satisfy the enablement requirement of the statute.

Applicants respectfully submit that the claims as presently amended are in condition for allowance. Accordingly, the above-noted rejection under 35 U.S.C. §112, first paragraph is, therefore, respectfully traversed.

THE CLAIMS AS AMENDED FULLY SATISFY THE REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has maintained the rejection of claims 9, 10, 12, 19, 22, 24, 27, 36, 37, 47 and 52 asserting that undue experimentation would be required to practice the invention as claimed. At page 3 of the Official Action, the Examiner acknowledges that the specification "enables antisense mediated inhibition of p66shc expression in vitro". However, the Examiner continues to maintain that the specification fails to enable practice of the present method in vivo. Claims 10, 22, 47 and 52 have been cancelled thereby rendering the rejection of these claims moot. Applicants have added new claims 53-62 to more particularly point out the subject matter regarded as the invention. For the reasons set forth below, Applicants continue to assert that the present specification provides sufficient disclosure to enable practice of the present method in vivo.

Claim 9 has been amended to recite a method for modulating oxidative stress resistance in a cell by reducing or preventing $p66^{shc}$ expression via contacting cells with an antisense molecule to $p66^{shc}$ to inhibit production of the p66 protein. The present inventors have discovered that disruption of the p66shc signaling pathway modulates the cellular response to oxidative stress. As such the present invention represents an advance in the state of the art of modulating $p66^{shc}$ mediated signal transduction. Claim 12 has been amended to recite the same features and new claim 58 has been added to more accurately reflect the subject matter that the Examiner has indicated as being fully enabled by the specification.

Applicants have described antisense molecules which are effective to down modulate $p66^{shc}$ expression and a method of use thereof to modulate cellular responses to oxidative stress. Applicants have also provided at page 20, lines 5-30 several means and references describing protocols for delivering antisense molecules of interest to target cells in vivo. The prior art demonstrates that antisense oligonucleotides can be administered via several routes to down modulate expression of the target nucleic acid in vivo. See Lu et al. (1993) who describe receptor mediated uptake of an antisense molecule via injection into the tail vein (Page 271, first column). Notably, this approach for delivery is provided in the specification at page 20, line 30. Also see Higgins et al. (1993) who describe delivery of an antisense molecule via subcutaneous administration (page 9901 bottom of second column); see Phillips et al. (1997) who describe AAV mediated delivery of an antisense molecule via direct injection of the vector comprising the antisense molecule into the brain of rats (page 376 second column). Notably AAV vectors are described in US Patent 5,252479 which is cited at page 20, line 19. The use of AAV vectors to deliver antisense

molecules is also disclosed in Hirao et al. (1999). See page 424, bottom of second column. Also see Puglielli et al. (1996) who describe liposome mediated transfer of an antisense molecule infused into the tail vein of rats. Additionally, Graham et al. (1997) disclose the in vivo distribution and metabolism of an antisense oligonucleotide administered via tail vein injection. Notably, these researchers disclose that significant intracellular delivery can be readily achieved in the liver after systemic administration. Each of these references is attached hereto for the Examiner's convenience. The prior art cited above provides a variety of protocols for the successful administration of antisense oligonucleotides in vivo. In each case where down modulation was assessed, the oligonucleotides administered, regardless of route of administration, exhibited measurable efficacy in down modulating target gene expression. In view of the foregoing, and the disclosure in the specification directing the skilled artisan to the approaches described above (page 20) it is submitted that the method encompassed by the present claims is fully enabled for practice both in vitro and in vivo.

The quantity of experimentation needed to determine the feasibility of using the full scope of this method, as presently claimed, may be regarded as extensive. However, the nature of the experimentation is quite routine and well within the capabilities of those skilled in the art. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). To the same effect is *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (ITC 1983), *aff'd. sub. nom, Massachusetts Institute of Technology* v. A.B. *Fortia*, 227 USPQ 428 (Fed. Cir. 1985), in which it was observed that the fact that experimentation may be complex does not necessarily

make it undue, if the art typically engages in such experimentation.

Once a target and effective antisense molecule have been identified, it routine to administer the antisense molecule in vivo, as taught in the present specification and exemplified in the prior art. The Examiner has cited references describing the unpredictability of antisense based therapeutic methods. In response, Applicants submit that as of Applicants' filing date, antisense molecules had been administered in vivo successfully and shown to down modulate target gene expression. Notably, claim 58 does not require a therapeutic effect per se, but merely requires the down modulation of $p66^{shc}$ via antisense administration. Claim 9 likewise does not require a therapeutic effect. The claim requires that administration of the antisense molecule alter oxdative stress response in treated cells relative to non-treated cells. Claim 12 recites that antisense administration alter p66shc signal transduction. In view of the literature cited above, and the disclosure provided in the specification, it cannot be reasonably maintained that practice of the invention requires undue experimentation.

At page 20, line 19, Applicants cite to US Patent 5,252,479 which describes a suitable AAV vector useful for delivery of the antisense molecules of the invention. It is without question that AAV vectors are effective to deliver heterologous nucleic acid molecules in vivo. See Phillips et al. and Hirao et al. cited above. One of skill in the art could readily clone the antisense molecule of the claims into such a vector in order to modulate the oxidative stress response in cells that take up the vector. Applicants are fully confident that inhibition of $p66^{shc}$ via antisense in vivo will result in a similar phenotype as that observed in the knock-out mice described in the specification. Moreover, means to assess this modulation are provided in Figure 9.

In the present case, the experimentation necessary is merely routine and is inherent in the nature of the art. Therefore, there is no undue burden of experimentation. The level of skill in the art of antisense administration is high as exemplified by the many citations provided herein and in Applicants' previous response. Moreover as the cited art demonstrates, the required techniques for administration of the same are familiar to those skilled in this art area.

Enablement must be assessed using the teachings in the specification as well as the knowledge of those skilled in the art at the time the application was filed. Clearly, methods for administering antisense oligonucleotides in vivo were known to the skilled artisan as evidenced by the references cited above. Nothing more is required to enable the presently claimed methods in vivo. In view of all the foregoing, Applicants submit that the invention can be practiced over the full scope of the claims. Accordingly, the rejection under 35 U.S.C. §112, first paragraph is inappropriate and should be withdrawn.

CONCLUSION

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

In the event a fee is required or an overpayment is made, the Commissioner is authorized to charge or credit the deposit account of the undersigned, Account No. 04-1406.

Early and favorable action on the present application is earnestly solicited.

Respectfully submitted,

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By 

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Enclosures: Graham et al. (1997)
Higgins et al. (1993)
Hirao et al. (1998)
Lu et al. (1993)
Phillips et al. (1997)
Puglielli et al. (1996)